Arterial Spin Labeling Measurements of Cerebral Blood Flow: A Review Emphasizing Pulsed versus Continuous Approaches

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ABSTRACT

Arterial spin labeling (ASL) refers to the use of endogenous arterial water as the perfusion tracer. To differentiate the tracer from the background tissue, the net magnetization of arterial water flowing proximally to the brain is modified with respect to the net magnetization of brain water. This review is focused on describing two basic approaches to obtain images of cerebral blood flow (CBF): pulsed ASL (PASL) and continuous ASL (CASL). Advantages and disadvantages to either approach are listed, along with potential sources of artifacts and pitfalls.

INTRODUCTION

Cerebral blood flow (CBF) can be measured by following the kinetics of a diffusible tracer as it perfuses the brain. In methods such as positron emission tomography (PET), single photon emission computerized tomography (SPECT) or quantitative autoradiography (QAR), the tracer is exogenously administered and is imaged against a quiet background, which has the advantages of high sensitivity and robustness of quantification, but also the disadvantages of being invasive and of providing generally poor spatial resolution due to the small amount of tracer used relative to the size of the brain. The same principles of tracer kinetics have laid the foundation for the use of MR-detectable, exogenously administered, diffusible tracers, such as $^{2}H_2O$, $CH^{19}F_3$, $H_2{}^{17}O$ or ^{129}Xe. However, the advantages of using an endogenous perfusion tracer, namely of proportioning a non-invasive method that allows repeated measurements of CBF to be performed indefinitely, motivated the development of arterial spin labeling techniques. Arterial spin labeling refers to the use of endogenous arterial water as the perfusion tracer. Unlike other methods for measuring CBF, in ASL the tracer is imaged against the brain water background. Therefore, the general principle behind the ASL techniques is to differentiate the net magnetization of arterial water flowing proximally to

the brain from the net magnetization of brain water. As the labeled water flows through the brain, a net decrease in magnetization is obtained due to the mixing (with or without exchange) between the existing local magnetization and the one from the freshly arrived labeled water, which is proportional to the flow rate. Therefore, this decrease in magnetization may be used to calculate CBF.

Traditionally, ASL techniques have been presented as belonging to one of two basic implementation categories. In the first approach, arterial water is continuously labeled proximally to the region of interest in the brain. This gives rise to a steady-state where the regional brain magnetization reaches a new equilibrium value governed by CBF in the form of the rate of arrival of labeled blood, by the magnetic relaxation rate of the labeling spins, and by the brain-blood water partition coefficient. This approach is referred to as *continuous ASL* (CASL). In the second approach, a single, yet large volume of arterial blood is dynamically labeled proximally to the region of interest and allowed to flow into the tissue prior to data collection. This approach is generally referred to as *pulsed ASL* (PASL). Both approaches will be described in detail in the following sections, and special emphasis will be given to advantages and disadvantages of either approach. In addition to the following material, ASL and other MR-based methods to measure CBF have been extensively reviewed in the literature (1-5).

GENERAL PRINCIPLES OF ASL

The formalism for ASL closely follows the one developed by Kety for monitoring the kinetics of freely diffusible tracers (6, 7). Following the Kety formalism, the brain tissue magnetization can be described by the Bloch equations, modified to include the effects of CBF:

$$\frac{dM_b(t)}{dt} = \frac{M_b^0 - M_b(t)}{T_{1b}} + CBF \cdot \left[M_a(t) - M_v(t)\right] \qquad [1]$$

where M_b is the brain tissue magnetization per gram of tissue, M_b^0 is the equilibrium value of M_b, T_{1b} is the longitudinal brain tissue relaxation time constant, *CBF* is the cerebral blood flow expressed in units of $\left[\frac{ml\ blood}{g\ tissue \cdot s}\right]$, and M_a and M_v are the arterial and venous blood magnetization per ml of blood. The above equation describes brain tissue as a single-compartment that is constantly receiving blood from the arterial side and losing blood water on the venous side. Assuming water to be a freely-diffusible tracer, the venous magnetization equals the brain magnetization according to:

$$M_v(t) = \frac{M_b(t)}{\lambda} \qquad [2]$$

where λ is the brain-blood water partition coefficient, defined as the ratio of the amount of water per gram of tissue and the amount of water per ml of blood. In equilibrium, the amount of water delivered by the arterial vasculature to the tissue compartment must equal the amount of water leaving that compartment on the venous side:

$$M_a^0 = M_v^0 = \frac{M_b^0}{\lambda} \quad [3]$$

Therefore, Eq. [1] can be rewritten as:

$$\frac{dM_b(t)}{dt} = \frac{M_b^0 - M_b(t)}{T_{1app}} - 2 \cdot \alpha(t) \frac{CBF}{\lambda} M_b^0 \quad [4]$$

with the apparent longitudinal relaxation time for tissue water in the presence of perfusion, T_{1app}, and the degree of labeling efficiency, $\alpha(t)$, defined as:

$$\frac{1}{T_{1app}} = \frac{1}{T_{1b}} + \frac{CBF}{\lambda}$$
$$\alpha(t) = \frac{M_a^0 - M_a(t)}{2M_a^0} \quad [5]$$

Equation [4] tells us a number of important things about ASL. First, to cause a change in brain tissue magnetization related to perfusion, one needs to label blood (i.e., $\alpha(t)$ must be different than zero). Second, the perfusion rate does not instantly change brain tissue magnetization, but it does so with a time constant given by T_{1app}. Third, because *CBF* is only on the order of 60 ml blood/100 g tissue-minute, $CBF/\lambda \approx 0.01$ s^{-1}, the impact of *CBF* on T_{1app} is much too small to allow *CBF* to be reliably measured from changes in relaxation rates. The following sections describe the different approaches to obtain *CBF* from Eq. [4].

CONTINUOUS ARTERIAL SPIN LABELING (CASL)

CASL was the first implementation of ASL (8, 9). In this approach, arterial water is continuously saturated ($\alpha \approx 0.5$) or inverted ($\alpha \approx 1.0$) proximally to the brain for a period long enough to allow the establishment of a steady-state in brain tissue magnetization. For a constant degree of labeling efficiency $\alpha(t) = \alpha$, a steady-state $M_b^{label} = M_b(t)\big|_{t>5T_{1app}}$ is reached in which:

$$\Delta M = M_b^0 - M_b^{label} = 2\alpha T_{1app} M_b^0 \frac{CBF}{\lambda} \quad [6]$$

Thus, the *CBF* rate can be obtained from two images obtained with ($\alpha \neq 0$) and without ($\alpha = 0$) labeling:

$$CBF = \frac{\lambda}{2\alpha T_{1app}} \cdot \frac{M_b^0 - M_b^{label}}{M_b^0} \quad [7]$$

In CASL, inversion of the arterial spins is preferred over saturation as the former produces twice the signal of the latter, and the most efficient way to achieve continuous inversion is to use a technique named flow-driven

adiabatic fast passage (AFP) (10). In AFP, a constant RF pulse of amplitude B_{1label} is applied off-resonance in the presence of a constant gradient G_{label} along the direction of flow in the arteries being labeled. The frequency-offset of the RF pulse is determined by the labeling gradient strength and by desired distance from the plane of inversion (called the labeling plane) to the magnet's isocenter. As they flow with velocity υ_a along the labeling gradient, the arterial spins experience a frequency sweep that mimics old continuous wave NMR experiments. As they pass through the labeling plane, they experience an adiabatic inversion which is maintained as they continue to flow away from the labeling plane. The conditions for this adiabatic inversion to occur are:

$$\frac{1}{T_{1a}}, \frac{1}{T_{2a}} << \frac{G_{label} \cdot \upsilon_a}{B_{1label}} << \gamma B_{1label} \qquad [8]$$

Equation [8] imposes several practical conditions to be fulfilled. One of the most important conditions is that the arteries must run in a fairly straight segment along the labeling gradient to cause a large enough frequency sweep. This imposes a significant constraint in which arteries can be efficiently labeled. For example, in humans, labeling must occur inferior to the Circle of Willis where the common carotid arteries and the internal carotid arteries are running in the inferior to superior (foot-head) direction. In addition, the inversion condition can only be satisfied for arteries with large enough velocities to experience a frequency sweep which is big with respect to the relaxation times of arterial blood, but small with respect to the amplitude of the RF pulse applied. Smaller arteries with lower flow velocities require the use of proportionally larger gradient strengths so that Eq. [8] is fulfilled. While it has been shown that the AFP process is very efficient (11), the degree of inversion at the labeling plane α_0 typically vary from 0.7 to 0.9 (12, 13).

Although the CASL approach is simple to implement, and produces high SNR compared to PASL approaches (see below), it has a few practical disadvantages that must be mentioned. Many MR scanners may not permit the continuous operation of their RF amplifiers. In addition, the continuous RF labeling may cause substantial RF power deposition in the subject. Although CASL images have been successfully obtained in humans at fields up to 7T, and in animals at fields up to 11.7T, SAR may constitute a limiting concern for the routine use of CASL at high magnetic field strengths.

Another complication of CASL is that it induces magnetization transfer (MT) effects (9, 14, 15). This occurs because application of long off-resonance RF pulses causes direct saturation of the macromolecular pool in brain tissue. Once saturated, this large macromolecular pool exchanges its magnetization with that of "free" tissue water, and effectively changes both T_{1app} and the equilibrium magnetization M_b^0. To overcome this problem, a distal labeling of the magnetization is performed in the control experiment to produce identical MT effects. This method works well for a single-slice positioned in the center between the proximal and the distal labeling planes. However, the long RF pulses used in such techniques are applied concurrently with the longitudinal labeling gradient, thus creating a spatial dependence of the MT effects dependent on the slice position. The two main undesirable consequences of MT effects are: (a) it reduces the observed signal and affects quantification of *CBF*; and (b) it

makes it difficult to obtain multi-slice or 3-D coverage of the brain. To overcome such difficulties, a few modifications of the original CASL approach have been proposed. Silva et al. proposed the use of a small separate labeling coil, placed on the neck to label the common carotid arteries (13). The field-of-view of the labeling coil is confined to the neck region and does not reach the brain, thus eliminating off-resonance effects, with the added benefit that it also greatly reduces the RF power deposition compared to a volume coil. The two-coil approach has also been successfully implemented in humans (16, 17). An alternative way to control for MT effects while allowing multi-slice acquisition was proposed by Alsop and Detre, who used a sinusoidal modulation of the control RF pulse (18, 19). The application of the amplitude modulated RF during the control phase of the experiment causes a dual inversion of the blood magnetization, resulting theoretically in negligible labeling during the control phase. To match the MT effects produced during the labeling phase of the experiment, the root mean square RF power is carefully adjusted during the control phase. However, imperfections in the double-inversion plane usually result in lower labeling efficiency (18).

PULSED ARTERIAL SPIN LABELING (PASL)

Unlike CASL, where arterial blood is continuously inverted in a well-defined and extremely thin labeling plane, PASL techniques rely on using a short RF pulse to invert all the water magnetization (blood and tissue) contained in a thick region or slab proximal to the brain. Several variants of PASL techniques have been proposed, as reviewed by Calamante et al. (2) and also by Barbier et al. (3). Following the inversion, blood in this slab flows into the region of interest and mixes with the non-inverted brain tissue water during an inflow time TI, at the end of which the image is acquired. The control image is acquired in the absence of the slab-selective inversion, so that subtraction of the two images according to Eq. [7], modified to include the relaxation of the brain tissue as well as of the arterial spins during the interval TI between application of the labeling inversion RF pulse and the signal acquisition (20, 21), results in a measurement of *CBF*:

$$\Delta M = 2\alpha M_b^0 \frac{CBF}{\lambda}\left[\frac{\exp\left(-TI/T_{1app}\right)-\exp\left(-TI/T_{1a}\right)}{\frac{1}{T_{1app}}-\frac{1}{T_{1a}}}\right] \qquad [9]$$

where T_{1a} is the T_1 of arterial blood. It is interesting to consider a special case when $T_{1a} \approx T_{1b} = T_1$, in which case Eq. [9] reduces to:

$$\begin{aligned} \Delta M &= 2\alpha TIM_b^0 \frac{CBF}{\lambda}\exp\left(-\frac{TI}{T_1}\right), \quad TI < \tau \\ \Delta M &= 2\alpha \tau M_b^0 \frac{CBF}{\lambda}\exp\left(-\frac{TI}{T_1}\right), \quad TI > \tau \end{aligned} \qquad [10]$$

where τ is the temporal width of the labeling slab. Eq. [10] has been commonly used to calculate *CBF* from PASL measurements. The maximum signal change occurs when $TI = T_{1app}$, in which case the PASL signal is only $e^{-1} \approx$ 37% of the signal obtained with CASL. The assumption of $T_{1a} \approx T_{1b}$ should be used with caution, however, given that there are cases when it is not valid, such as when measuring perfusion in white matter or in pathological cases, such as in the measurement of tumor blood flow. In such cases Eq. [9] provides a more accurate estimate of *CBF*.

The main advantages of PASL over CASL are the closer proximity of the inversion labeling slab to the region of interest, which tends to minimize transit time effects, when a good definition of the trailing edge of the bolus of label can be achieved. In addition, MT effects are smaller due to the use of short RF labeling pulses, compared to the long continuous pulses used in CASL. The main disadvantage of PASL is a reduced sensitivity to flow, since the inverted blood water relaxes during the inflow time.

PITFALLS IN ASL

A detailed comparison of CASL and PASL techniques can be found in (22). In a nutshell, the major advantage of CASL techniques is the higher SNR compared to PASL (theoretically about 2.7 fold, comparing Eq. [7] to Eq. [10]), combined with a higher overall degree of labeling efficiency because the labeling plane can, on average, be placed closer to the region of interest compared to the thick labeling slabs required in PASL. On the other hand, the major advantage of PASL techniques is the lower RF power deposition compared to CASL, an advantage that can become really important at high magnetic field strengths, such as 7T and above.

A few pitfalls afflict the implementation of both CASL and PASL techniques. Knowledge of such sources of error is important to ensure optimal application of either approach.

Transit-time

In both CASL and PASL approaches, labeled blood must flow from the labeling location to the region of interest. This happens in a non-negligible amount of time called the transit-time, δ. During the transit-time, labeled water is relaxing with a time constant T_{1a}, so that the major effect of the transit-time is to decrease the effective degree of labeling efficiency, $\alpha(t)$ as given by Eq. [5], which now turns into:

$$\alpha(t) = \alpha_0 \exp\left(-\frac{\delta}{T_{1a}}\right) \qquad [11]$$

where α_0 is the degree of labeling efficiency measured at the labeling plane for CASL or averaged over the inversion slab for PASL. Relaxation of the label due to a non-negligible transit-time imposes an exponential decay of the MRI signal for CASL and a linear decay for PASL:

$$\Delta M_{CASL} = 2\alpha_0 \exp\left(-\frac{\delta}{T_{1a}}\right) T_{1app} M_b^0 \frac{CBF}{\lambda} \qquad [12]$$

$$\Delta M_{PASL} = 2\alpha_0 (TI - \delta) M_b^0 \frac{CBF}{\lambda} \exp\left(-\frac{TI}{T_1}\right) \quad [13]$$

While δ is on the order of 250-300 ms in rats (14), it can be equal to T_{1a} in humans and thus significantly affects the signal. Fortunately, a relatively simple modification of the standard CASL and PASL techniques can be implemented to minimize the effects of transit-time on the quantification of perfusion. For CASL, the introduction of a post-labeling delay $w \geq \delta$ between the end of the labeling period and the image acquisition allows for all the labeled blood to enter the tissue prior to image acquisition (23). In order to minimize the presence of labeled blood in the arterial vessels, it is important to set the post-labeling delay longer than the longest transit-time. An additional advantage of the post-labeling delay is that it allows most of the intravascular signal from labeled blood that is destined to regions of the brain other than the region of interest to wash out prior to image acquisition. In this way, vascular volume artifacts are minimized. For PASL, the requirement for all the labeled blood to enter the region of interest is that $TI > \tau + \delta$. Unfortunately, it is hard to control the temporal width of the volume of labeled water, since it depends on the spatial extent of the inversion slab, on the flow and on the geometry of the proximal vessels. To alleviate this problem, a pulse sequence named QUIPSS II was implemented (24) in which a saturation pulse is applied at a time T_{sat} after the inversion of the same slab. The saturation defines the temporal width of the inverted slab to be $\tau = T_{sat}$.

Residual Intra-Vascular Labeled Water

The presence of residual labeled blood in the arteries can cause overestimation of *CBF* and introduce image artifacts in the form of bright spots. This vascular signal contamination comes from large vessels in which blood is merely passing through the region of interest on its way to perfuse other distal areas. One possible solution to eliminate the signal from these larger vessels consists of applying flow-sensitive crusher gradients (9, 25). However, the application of strong bipolar gradients may also attenuate the flow-related signal, so it must be employed with great caution. Alternatively, the use of a post-labeling delay as described above can be very effective in removing vascular volume artifacts.

Motion Artifacts

Because ASL techniques require the subtraction of two images acquired at different time points, in which the desired flow-related signal is only a few percent the signal of the control and of the labeled image, the presence of motion can significantly degrade image quality and lead to large errors in *CBF*. This problem can be much reduced by the use of ultra-fast imaging sequences, such as EPI or SPIRAL imaging. Furthermore, because the control and the labeled images are acquired in an interleaved manner, the effects of motion can be significantly attenuated. Recently, the use of background suppression has been proposed as an alternative way to minimize the influence of motion on ASL (26-28).

The Effects of Restricted Exchange and Multiple Compartment Modeling

It has been observed that water can not be considered a freely diffusible tracer in a strict sense. At normal perfusion rates, about 90% of the arterial water leaves the capillaries and exchanges with tissue. However, this fraction falls to less than 50% at high flows (29). Therefore, a significant improvement of the original ASL formalism is to consider the effects of restricted water exchange between the intravascular and the extravascular compartments, manifested in the form of finite capillary water permeability. In addition, the presence of labeled water in capillaries and veins should be considered as well. There has been considerable effort in the recent years in this direction (30-35).

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